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ORIGINAL ARTICLE

Brain Anatomic Magnetic Resonance Imaging in Childhood-Onset Schizophrenia

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Background: Early-onset schizophrenia (first psychotic symptoms by age 12 years) has been the subject of a small number of studies, and its biological continuity with later-onset disorder has not been established. In this study, quantitative anatomic brain magnetic resonance images of children and adolescents with early-onset schizophrenia were compared with those of matched controls. Brain abnormalities in childhood-onset schizophrenia were examined in relation to those reported for later-onset schizophrenics.

Methods: Anatomic brain magnetic resonance imaging scans were obtained for 21 patients (mean±SD age, 14.6±2.1 years; range, 10 to 18 years) with childhood-onset schizophrenia (13 males, eight females) and 33 age-, sex-, height-, and weight-matched normal controls. Quantitative measurements were obtained for the cerebrum, anterior frontal region, lateral ventricles, thalamus, caudate, putamen, and globus pallidus.

Results: Total cerebral volume and midsagittal thalamic area were smaller in the patients (analysis of variance, $P=.002$, and analysis of covariance, $P=.03$, respectively); the caudate, putamen, and globus pallidus were larger in the patients (analysis of covariance, $P=.05$, $P=.007$, and $P<.001$, respectively); and the lateral ventricles tended to be larger in the patients (analysis of covariance, $P=.06$). Globus pallidus enlargement correlated with neuroleptic exposure and with age of onset of psychosis. The magnitude of abnormalities compared with controls was similar to that reported in adult studies, although there was a trend toward relatively smaller cerebral volumes for the childhood-onset group compared with controls.

Conclusion: Brain anatomic abnormalities in childhood-onset schizophrenia are similar to those reported for adult populations, indicating overall continuity between these rare childhood cases and the adult schizophrenia populations.

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CHILDHOOD-ONSET schizophrenia (defined as onset of psychotic symptoms by age 12 years, the age of pubertal onset)[1,2] is rare, having 1/50th the prevalence of later-onset disease.[3-6] An apparent increased prevalence prior to the 1970s was probably caused by psychotic disorders of childhood (including autism) being diagnosed as childhood schizophrenia. In 1971, Kolvin and colleagues' landmark studies[7] distinguished autism (psychosis before age 3 years) from schizophrenia (psychosis after age 5 years). Several subsequent studies have also documented very-early-onset schizophrenia as symptomatically similar to the adult-onset disorder.[2,8-11] However, it remains unknown whether childhood-onset schizophrenia reflects a pathophysiologic process separate from or continuous with adult schizophrenia.[7-8,11-14]

Clinical and neuropsychological studies of childhood-onset populations present compelling evidence for continuity, but there have been few neurobiological investigations of the disorder. In schizophrenic adults, there is considerable evidence for abnormal brain anatomy; most consistently, reduced medial temporal lobe, enlarged ventricles, dilation of the third ventricle, and smaller brain volume, with recent reports of enlarged basal ganglia and thalamic abnormalities.[15-28] Brain magnetic resonance imaging (MRI) measures therefore are particularly relevant to the question of continuity between early- and later-onset cases.

Only a few case reports and studies with small numbers of patients have addressed brain developmental patterns in childhood-onset cases.[29-31] Woody and colleagues[29] (1987) described a 10-year-old prepubertal boy with well-documented *DSM-III* schizophrenia whose MRI showed enlargement of the ventricles and cisterna magna with a hypoplastic (or atrophied) left cerebellum. Hendren and colleagues[31] (1991)

See Methods on next page

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METHODS

SUBJECTS

Subjects were recruited nationally through professional and patient advocacy groups for an inpatient study involving a double-blind trial of haloperidol and clozapine.[32] Inclusion criteria were *DSM-III-R* diagnosis of schizophrenia,[33] psychotic symptoms documented by age 12 years, age 6 to 18 years, and full-scale IQ score of 70 or above. Medical or neurological diseases were exclusionary. Subjects had to have had at least two unsuccessful previous neuroleptic trials because of either intolerable side effects or nonresponse, as required for clozapine treatment.

From 450 charts, 105 patients and their families were screened in person. Admission to the study followed a 6-hour meeting, including review of old charts, clinical interviews with parents and child, and structured interviews using sections of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version[34] and the Diagnostic Interview for Children and Adolescents, Revised.[35] Those with a primary diagnosis of major affective disorder with psychotic features were excluded. Seventy-five children and adolescents who did not meet *DSM-III-R* criteria for schizophrenia were excluded after the screening process. Thirty children received the diagnosis of schizophrenia. Four children did not participate because of parental decision and two children were determined to have onset of psychosis after age 12 years during the screening and did not qualify for the study. Twenty-four of the 30 children have been studied to date.

Magnetic resonance imaging scans were obtained for 21 of the 24 enrolled patients; one patient was unable to comply with the scanning process and two others had not yet been scanned at the time this report was written. Thirteen patients were male and eight were female. Their mean±SD age at admission was 14.6±2.1 years (range, 10 to 18 years), and their mean age of onset of psychosis was 10.2±1.5 years (range, 7 to 12 years). All patients were pubertal at the time of admission (mean±SD Tanner score, 3.9±1.1; range, 2 to 5).[36] The group had considerable prior neuroleptic therapy (24.3±17.5 months) and hospitalization (8.0±10.6 months). Three (14%) of the 21 patients had a first-degree relative with definite or probable schizophrenia. Parents had considerable education. Eleven (52%) of the fathers and nine (43%) of the mothers had at least partial college training. The socioeconomic status was generally middle class. The mean full-scale IQ (FSIQ) score for the 14 patients who could be tested at the NIH was 82.1±16.8. Seven patients could not be adequately tested because of the severity of their illness and inability to comply, although all had demonstrated normal educational and developmental achievement before onset of psychosis, with a mean FSIQ of 87.3±16.6 for the seven subjects who had formal testing on the Wechsler Intelligence Scale for Children–Revised (WISC-R) prior to their arrival at the NIH. Rating scores on the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), and Bunney-Hamburg psychosis subscale during the fourth week of the drug-free period were obtained on all subjects and used in correlational analyses involving all measured brain structures that differed significantly between patients and controls.[37-40] Interrater reliabilities (intraclass correlation [ICC]) assessed by two separate sets of child psychiatrists at two separate points in the study (C.T.G. and K.M., and K.M. and J.A.F.; one physician was consistent across both reliability assessments) were .64 and .90 for the BPRS, .81 and .92 for the SANS, .91 and .87 for the SAPS, and .81 and .91 for the Bunney-Hamburg psychosis subscale.

Thirty-three healthy comparison subjects (mean age, 14.6±1.6 years; 22 male and 11 female) matched for age, sex, and handedness were recruited from the community through advertisements.[26,41] There were no significant height, weight, or Tanner stage differences between the groups. Screening procedures included a physical and neurological examination; Child and Parent Diagnostic Interview for Children and Adolescents[42]; Child Behavior Checklist[43]; the Vocabulary, Block Design, and Digit Span subtests of the WISC-R; Connors parent and teacher questionnaires[44,45]; and the 12 handedness items from the Physical and Neurological Examination for Subtle Signs.[46] Any physical or neurologic disorder, a lifetime history of any psychiatric disorder, or a history of major psychiatric disorder in first-degree relatives was exclusionary. Subject and control characteristics are summarized in **Table 1**.

The study was explained to the subjects and their parents. Written assent was obtained from the child and written informed consent from the parents. The protocol was approved by the Institutional Review Board at the National Institute of Mental Health, Bethesda, Md.

DRUG EXPOSURE

Antipsychotic doses at the time of admission and total lifetime antipsychotic exposure (summed doses×length of trials) were obtained via chart review and converted to chlorpromazine equivalents for correlational analyses.[47]

MRI PROTOCOL

Subjects were scanned on a 1.5-T Signa scanner (General Electric, Milwaukee, Wis) located at the NIH Clinical Center, Bethesda, Md. A three-dimensional spoiled gradient recalled echo in the steady-state imaging sequence (time to echo, 5 milliseconds; time to repeat, 24 milliseconds; flip angle, 45°; acquisition matrix, 192×256; number of excitations, 1; and field of view, 24 cm) was used to obtain T_1-weighted images with a slice thickness of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane. Head position was controlled for using vitamin E capsules as external markers (one in the meatus of each ear and one taped to the left inferior orbital ridge, assuring that all three were visible in the same axial reference plane). Rotation in the other plane was controlled by aligning the nose to the 12-o'clock position. Head movement was minimized by placing foam padding on the sides of the subjects' heads. Scans were performed in the evening to promote subjects falling asleep in the scanner. Sedation with chloral hydrate (1.5 to 2.0 g by mouth) or lorazepam (1.0 to 2.0 mg by mouth) was used for seven childhood schizophrenia subjects.

IMAGE ANALYSIS

A neuroradiologist reviewed all scans. No abnormalities were noted for the control group. Clinical MRI readings of the

childhood-onset schizophrenia group recorded enlargement of the left lateral ventricle for one subject and a focal area of increased signal in the left frontal white matter for one other subject. These subjects were retained in the data set. An image analysis program (Image 1.6) developed at the NIH was used.[48] All MRI scans of subjects and controls were rated blind.

Cerebral Volume

Brain spatial orientation was first standardized using the midline anterior and posterior commissures and the interhemispheric fissure. A novel image analysis technique, using an active surface template of the brain to incorporate prior knowledge of brain anatomy to supplement MRI signal intensity characteristics, was then employed to quantify the left and right cerebral hemispheres. This method models the brain surface as an elastically deformable structure while using successive iterations of an energy minimization function to enforce constraints on curvature and topology. After this procedure, the images were edited in the axial plane slice by slice by experienced raters to remove remaining artifacts, such as eyeballs or patches of dura. Intraclass correlations for the volumes of the edited brains were .99 for interrater reliability and .95 compared with volumes derived from more conventional slice-by-slice manual tracing technique through all axial slices on which brain matter is visible (**Table 2**). Further details are provided elsewhere.[49,50]

Anterior Frontal Volume

A region designated as "anterior frontal" was defined as all brain matter anterior to a coronal plane intersecting the anterior-most point of the corpus callosum. The orientation of the plane was further standardized to be perpendicular to a line connecting the midline anterior and posterior commissures. Interrater ICC for this semiautomated measure was .97.

Lateral Ventricle Volume

Lateral ventricular volumes were calculated by summing area measurements from all coronal planes on which ventricles were visible using an operator-supervised thresholding technique available in the Image 1.6 program.[48] Because of the semiautomated technique and clear distinction of cerebrospinal fluid from surrounding tissue, interrater reliability was extremely high (ICC, .99).

Subcortical Gray Matter Volumes

The caudate and putamen were manually outlined from all coronal slices on which they were visible. Both structures were traced along the gray matter–white matter border, and along the ventricle–gray matter border for the medial aspect of the caudate. The tail of the caudate, defined as the portion inferior to the head and body, was not included, nor was the nucleus accumbens. Since the sum of areas from the odd-numbered slices for the first 20 subjects correlated highly with the sum of the areas from the even-numbered slices (ICC, .98), subsequent outlining was done on every other slice and then multiplied by a slice thickness of 4 mm to derive volume. Interrater reliability (ICC, .88 and .84 for the caudate and putamen, respectively) was assessed initially and then periodically during the analyses to monitor potential "drift" in operator measurements.

The globus pallidus was also measured on coronal sections, but this measurement included every slice, beginning 2 mm anterior to the anterior commissure and proceeding posteriorly for a total of 14 mm. Our methods were not sufficient to differentiate internal from external components of the globus pallidus. Limiting sampling to the 14-mm domain described improved interrater reliability (ICC, .86) and encompassed the entire globus pallidus in the majority of subjects.

A symmetry index of basal ganglia structures was calculated by the following formula: (right−left)/[(right+left)/2].

Because volumetric quantification of the thalamus is beyond our current methods, the thalamus was manually outlined from a single midsagittal slice reconstructed from the axial series. Reslicing from the axial series allows more precise designation of the midsagittal plane than choosing a "best" midsagittal slice from the sagittal series. The ICC of interrater reliability for the thalamic area was .85.

DATA ANALYSIS

To examine group differences between patients and controls, *t* tests, analyses of covariance (ANCOVA), and χ^2 analyses were used, depending on data distribution and type. Comparisons were made on all demographic variables (gender, age, height, weight, Tanner stage, handedness, and cognitive measures) as well as the absolute values of the brain regions of interest. Because the childhood-onset schizophrenia cohort had significantly smaller total cerebral volume, ANCOVA controlling for cerebral volume was used in one-way or two-way (group-by-side) repeated-measures analyses, with Duncan post hoc comparisons. The Statistical Analysis System[51] was used for the above procedures. Pearson correlations were computed between (1) patient MRI measures with values significantly different from those of controls and (2) clinical measures, including age at study; age of onset; duration of illness; FSIQ score; week 4 off-drug baseline ratings on the SANS, SAPS, BPRS, and Bunney-Hamburg psychosis subscale; and neuroleptic exposure in chlorpromazine equivalents (admission and lifetime).

All tests were two-tailed, and the Greenhouse-Geiger correction factor was used where appropriate. $P=.05$ constituted significance, and $P<.1$ constituted a trend.

Standardized scores (*z* scores) were created for anatomic brain measures that were statistically different from those of controls; *z* scores were also created for the analagous structures reported for adults, to compare the degree of deviance for adult and child patients relative to their respective control groups.[18-21,24-26,28] For each structure, adult MRI studies done at different academic centers were chosen for comparison. Each study was done on a 1.5-T scanner and had a relatively large number of subjects ($n \geq 25$). A *z* score was created for each adult study, and then a mean *z* score was calculated for each structure. A *z* score difference between adults and children was calculated using the following formula: (mean adult *z* score−mean child *z* score)/$\sqrt{2}$.[52]

Table 1. Demographic Characteristics of Patients With Childhood-Onset Schizophrenia and Healthy Controls*

Measure	Schizophrenics (n=21)	Normal Controls (n=33)	P (t test)
Age, y	14.6 (2.1)	14.6 (1.6)	.65
Height, cm	164 (10)†	166 (14)	.52
Weight, kg	61.2 (17.6)	56.1 (11.8)	.17
Tanner stage	3.9 (1.1)	3.8 (1.4)	.78
Right-handed, No. (%)	15 (71)	28 (85)	.20‡
WISC-R subtests			
Vocabulary	7.3 (3.3)§	12.9 (2.8)	<.001
Block Design	9.4 (4.3)‖	13.3 (2.8)	<.001
Age at onset of psychosis, y	10.2 (1.5)	...	...
Neuroleptic exposure, mo	24.3 (17.5)	...	...
Hospitalization, mo	8.0 (10.6)	...	...
Age at first hospitalization, y	11.8 (2.2)	...	...

*Unless otherwise indicated, values are mean (SD). WISC-R indicates Wechsler Intelligence Scale for Children–Revised.
†n=20.
‡χ^2=1.7.
§n=15.
‖n=14.

completed quantitative MRIs for 37 psychiatric inpatients (age 5 to 14 years), but only six carried schizophrenia "spectrum" diagnoses (including schizophrenia, schizophreniform disorder, and other psychosis). Interestingly, three of six psychotic children had larger left ventricular frontal horns than did a comparison group of 31 children with other diagnoses. Similarly, Schultz and colleagues[30] (1983) reported ventricular enlargement in 15 schizophrenic/schizophreniform patients (mean±SD age, 16.5±1.7 years, with a mean duration of illness of 13 months), with no correlation with duration of illness or prior treatment.

The present report is on anatomic brain MRI morphologic characteristics of a group of children and adolescents with schizophrenia who had onset of psychotic symptoms by age 12 years.[12-14] Quantitative MRI measures of basal ganglia, thalamus, ventricular size, ventricular brain ratio, anterior frontal volume, and total cerebral volume are reported for the first 21 cases scanned at the National Institutes of Health (NIH). Based on the similar phenomenologic characteristics and family history pattern in this cohort and adult cohorts,[12] the authors hypothesized that there would be an anatomic brain pattern similar to that seen in adult populations. We further speculated that there might be more striking or severe brain abnormalities in this cohort as a possible explanation for the unusual age of presentation.

See also pages 574, 577, 585, 595, 607, and 625

RESULTS

Compared with controls, patients with childhood schizophrenia had a smaller cerebral volume, and even when the smaller cerebral volume was taken into account with ANCOVA, they had a smaller thalamic area, robust increases in basal ganglia volumes, and a larger lateral ventricular volume. These results are summarized in **Table 3** and **Table 4**.

Table 2. Childhood-Onset Schizophrenia Brain Magnetic Resonance Imaging Study Reliabilities for Operator-Assisted Measures

Structure	Intraclass Correlation Coefficient	
	Intrarater	Interrater
Cerebrum	.98	.99
Anterior frontal	.98	.97
Ventricles	.99	.99
Caudate	.89	.88
Putamen	.85	.84
Globus pallidus	.86	.82
Thalamus (area)	.86	.85

VOLUME MEASUREMENTS

Cerebrum

Schizophrenic children had a total cerebral volume 9.2% smaller than that of normal controls (t=3.01, df=52, P=.004). Both the right and left hemispheres were smaller than in normal controls (t=2.64, df=51, P=.004, and t=2.99, df=51, P=.01, respectively). Males had greater total cerebral volume than females in both the study and normal control groups (t=3.7, df=19, P=.002, and t=2.9, df=31, P=.006, respectively).

Anterior Frontal

Anterior frontal volume did not differ significantly between groups.

Ventricles

Schizophrenic subjects had a trend toward larger lateral ventricles bilaterally than controls (F[1, 50]=3.61, P=.06). The ventricular brain ratio was increased for schizophrenics (t=2.22, df=51, P=.03).

Subcortical Structures

All basal ganglia structures were enlarged in the patient group (Table 4). Subjects with schizophrenia had a larger total caudate than normal controls (ANCOVA: F[1, 50]=4.07, P=.05), predominantly on the left side. The normal caudate asymmetry (right greater than left) was decreased for patients (t=2.21, df=28, P=.04), the only significant asymmetry difference observed in this study.

Study subjects had a robust increase in globus pallidus total volume (F[1, 51]=16.07, P<.001). Finally, the putamen was larger for subjects with schizophrenia (F[1, 50]=5.44, P=.007).

Thalamus

The midsagittal area of the thalamus was 17.2% smaller for subjects with schizophrenia (t=2.82, P=.007; ANCOVA: F[1, 52]=5.44, P=.02).

Table 3. Mean Brain Volumes for Patients With Childhood-Onset Schizophrenia (n=21) and Normal Controls (n=33)

	Volume			
	Unadjusted Mean (SD)		Adjusted Least-Square Mean*	
Structure	Schizophrenics	Controls	Schizophrenics	Controls
Ventricles				
Right	7.06 (3.2)	5.87 (3.0)	7.40	5.66
Left	8.45 (4.5)	6.83 (3.4)	8.79	6.62
Anterior frontal				
Right	71.8 (26.2)	84.0 (14.7)	78.4	79.9
Left	71.4 (11.9)	82.9 (14.9)	74.7	80.8
Caudate				
Right	5.05 (0.7)	5.07 (0.6)	5.22	4.97
Left	5.03 (0.5)	4.89 (0.6)	5.20	4.79
Globus pallidus				
Right	1.49 (0.2)	1.31 (0.2)	1.52	1.29
Left	1.38 (0.2)	1.20 (0.2)	1.41	1.18
Putamen				
Right	5.67 (0.8)	5.49 (0.6)	5.86	5.38
Left	5.67 (0.8)	5.46 (0.8)	5.86	5.35
Thalamus (arca)	120.70 (29.5)	148.83 (39.1)	122.39	147.75
Cerebrum	1049.7 (116.8)	1155.9 (132)	...	...

*Adjusted for total cerebral volume.

Table 4. ANOVA and Repeated-Measures ANCOVA for Brain Volumes in Childhood-Onset Schizophrenia*

		Diagnosis		Side Effects		Diagnosis × Side Effects	
Structure	Test†	F	P (2-Tailed)	F	P	F	P
Anterior frontal	ANOVA	10.14	.003 (N>S)	2.07	.16	0.02	.90
	ANCOVA	2.07	.16				
Ventricles	ANOVA	2.23	.14	12.16	.001 (L>R)	0.40	.53
	ANCOVA	3.61	.06 (S>N)				
Caudate	ANOVA	0.16	.69	8.27	.006 (R>L)	5.05	.03 (S: R=L, N: R>L)
	ANCOVA	4.07	.05 (S>N)				
Globus pallidus	ANOVA	11.12	.002 (S>N)	32.44	<.001 (R>L)	0.01	.94
	ANCOVA	16.07	<.001 (S>N)				
Putamen	ANOVA	1.07	.31	0.29	.59	0.20	.66
	ANCOVA	7.78	.007 (S>N)				

*ANOVA indicates analysis of variance; ANCOVA, analysis of covariance; S, schizophrenics; and N, normal controls.
†The ANCOVA covaries for total cerebral volume.

COMPARISON WITH REPORTS ON LATER-ONSET DISORDER

The z score comparison of the effect size of differences from controls in brain volumes between this childhood-onset cohort and adult-onset schizophrenia studies showed no significant differences (P=.09 to .94) (**Table 5**). There was a trend, however, toward a difference from adults for the total cerebral volume in this cohort (P=.09). While the thalamic area was decreased in the childhood-onset schizophrenia patients, the difference from adult patients was not significant.

CLINICAL CORRELATES

Clinical correlates were evaluated for all MRI measures that differed significantly from control values. Seven correlations were significant (**Table 6**). There was a significant negative correlation between total cerebral volume and week 4 off-drug rating for negative symptoms with the SANS and with the Bunney-Hamburg psychosis subscale. The putamen showed a negative correlation with week 4 off-drug Bunney-Hamburg psychosis subscale score. The thalamic area also demonstrated a negative correlation with negative symptoms on the SANS. Most notable was the consistent relationship between globus pallidus volume and chlorpromazine equivalent medication dose at admission, age at time of study, and age of onset. There also was a trend toward a negative correlation between caudate volume and chlorpromazine equivalent medication dose at admission and total lifetime chlorpromazine equivalent dose.

COMMENT

Anatomic MRI brain measures of children with very-early-onset schizophrenia exhibit a pattern of abnormali-

ties similar to that reported for adult populations. Children with early-onset schizophrenia have smaller cerebral volumes, smaller thalamic area, and enlarged basal ganglia structures, with a trend toward enlarged ventricles. Similar findings have been amply documented in adults.[17,19,20,23-28,53-65]

The effect size found in this cohort was generally similar to that observed for adult populations. Standardized differences were compared using z scores; this was the only way to directly compare measures of the child cohort with measures in adult cohorts. This type of comparison, however, is crude at best because of numerous methodological differences between studies.

The trend toward smaller total cerebral volume (using z score comparison) in this cohort suggests that children with schizophrenia may have a bigger lesion compared with their controls than is the case among adults with schizophrenia compared with their controls. The trend toward smaller total cerebral volume may indicate a greater central nervous system insult in the population with very-early-onset schizophrenia that might predispose these children to early development of psychotic symptoms. However, this trend toward smaller total cerebral volume is confounded by the lower IQ score and possible selection bias in this childhood-onset schizophrenia cohort.

A limitation of the study is that the schizophrenic children and normal controls could not be matched on IQ score, given the relatively poor performance of the cohort on the WISC-R vocabulary subtest. This is a potential confounding factor, as in normals there is an established relationship between IQ score and brain size.[41] However, the possible relationship between lower IQ score and smaller brain size is not necessarily a confounding factor, as lower IQ score may be an integral manifestation of the disorder, with its compromise in brain function and thought processes. In the childhood-onset schizophrenia cohort there was no correlation between scores on the WISC-R subtests and total cerebral volume, although there was a positive correlation between scores on both the Vocabulary and Block Design subtests and total cerebral volume in the control group. Also, the healthy subjects were likely to have higher-than-average WISC-R subtest scores because of our strict exclusion criteria for neurologic, medical, or psychiatric illness.

In addition, all of our subjects were nonresponders to typical neuroleptic therapy, which may mean we selected patients with inherently more severe illness. Crow,[66] for example (1985), has suggested that neuroleptic nonresponders may have greater brain abnormalities than neuroleptic responders. However, while the present cohort was severely ill, the phenomenologic characteristics, sex ratio, and premorbid histories of this population[67] resembled those described for more "typical" childhood cohorts.[2,7-10] Therefore, our findings may in fact be representative of children with schizophrenia.

The enlargement of the globus pallidus showed some relationship to current and previous medication therapy. Because of the number of correlations run on these data, a number of correlations would have been expected to be significant by chance. However, there is a consistent pattern of association between drug exposure and volume of the globus pallidus. Chakos and colleagues[23]

Table 5. Comparison of Effect Size of Differences From Normal Controls of Brain Volumes Between Adults and Children With Schizophrenia

Structure	z Score: Adult	z Score: Child	z Score: Difference*	P (2-Tailed)
Total cerebral[19, 21, 28]	−0.74	−3.09	1.67	.09
Ventricles[18, 21, 26]	2.62	1.47	1.15	.25
Thalamus[18, 26]	−0.92	−3.0	1.47	.14
Caudate[21, 24-26]	0.52	0.41	0.08	.94
Putamen[24, 25]	1.62	0.87	0.53	.60
Globus pallidus[24]	2.44	4.0	1.11	.27

*(Mean Adult z Score − Mean Child z Score)/$\sqrt{2}$.

Table 6. Clinical Correlates of Anatomic Brain Volume Measurements for Childhood-Onset Schizophrenia (n=21)*

Correlate	r/P: Total Cerebral	Ventricular Brain Ratio	Ventricles	Globus Pallidus	Caudate	Putamen	Thalamus
Age at study	.03/.91	−.29/.22†	−.27/.26†	**.48/.03**	−.20/.40†	.08/.75†	.19/.43
Age at onset	−.16/.50	−.30/.21†	−.24/.32†	**.53/.01**	−.04/.88†	.15/.54†	−.27/.24
Duration of illness	.08/.73	−.26/.28†	−.28/.24†	.22/.35	−.18/.44†	.05/.82†	.18/.43
Chlorpromazine equivalent at admission	−.12/.61†	.19/.43†	.15/.53†	**.49/.03†**	−.42/.07†	−.13/.60†	.11/.65†
Lifetime chlorpromazine equivalent	−.33/.17†	.11/.66†	.02/.94†	.30/.20†	−.41/.08†	−.07/.77†	.04/.88†
Full-scale IQ score	−.03/.92‡	−.21/.46§	−.16/.59§	.02/.95‡	.25/.38§	.14/.62§	−.11/.69‡
Brief Psychiatric Rating Scale total score	−.26/.17†	.10/.69‖	.01/.97‖	.36/.12†	−.26/.29‖	−.13/.60‖	−.06/.82†
Scale for the Assessment of Negative Symptoms total score	**−.63/.004‖**	−.05/.84¶	−.16/.52¶	.36/.13‖	−.14/.58¶	−.39/.11¶	**−.57/.01‖**
Scale for the Assessment of Positive Symptoms total score	−.41/.08†	.17/.48‖	.09/.71‖	.30/.20†	−.35/.14‖	−.07/.79‖	−.24/.31†
Bunney-Hamburg psychosis subscale score	**−.50/.02†**	−.15/.54‖	−.23/.35‖	.13/.60†	−.29/.24‖	**−.54/.02‖**	−.31/.18†

*Boldface indicates significant correlation.
†n=20.
‡n=15.
§n=14.
‖n=19.
¶n=18.

(1994) report a similar relationship between prior medication and caudate volume.

Animal studies have shown clear microscopic effects of typical neuroleptics in the striatum, with hypertrophy of mitochondria and small increases in neuronal cell size and striatal terminals.[68-70] Additionally, rat studies indicate that microscopic changes seen in the striatum are at least partially reversible with drug washout.[68] Typical neuroleptics and atypical neuroleptics, such as clozapine, affect different receptor populations[71] and have different effects on release of γ-aminobutyric acid in the basal ganglia.[72] In keeping with these preclinical data and the recent report by Chakos and colleagues[73] of differences in caudate volume in patients who underwent MRI scans while taking typical antipsychotics and then underwent rescanning while taking clozapine, there is also some evidence of basal ganglia normalization for a subset of patients in our cohort who underwent rescanning after 2 years of clozapine maintenance therapy.[74]

The association of enlarged globus pallidus with later age of onset is interesting. However, because there is no significant correlation between age of onset and neuroleptic dose, the association between neuroleptic dose at admission and globus pallidus size remains significant.

Alternatively, larger basal ganglia volumes in the present cohort might be seen as representing "abnormal pruning" in the patient population.[75-79] This appears unlikely, however, because the increase in volume occurs in structures that do not change at puberty in the normal child population (globus pallidus) as well as in those that do (putamen and caudate).[49]

The finding of smaller thalamic area is consistent with the recent findings of smaller thalamic area[28] and thalamic abnormalities[27] in adult patients. As discussed by Andreasen et al[27] (1994), lesions in the midline thalamus might explain complex symptoms involved in the psychotic process of schizophrenia, given the role of the thalamus in filtering sensory input.

Finally, we do not believe that these data reflect a nonspecific pattern for neurodevelopmentally impaired children. A large cohort of 60 males with attention deficit hyperactivity disorder (aged 4 to 18 years) and matched controls examined with identical procedures did not share the pattern of abnormalities seen in the present study.[80,81] This ADHD contrast group is particularly relevant, as six patients (29%) in this cohort had clear signs and symptoms of attention deficit hyperactivity disorder premorbidly.[67]

Further research on these rare cases will have important implications for later-onset schizophrenia. Given substantial data supporting a neurodevelopmental basis for schizophrenia,[82-89] the findings of this study raise important questions about whether there is evidence for late brain maturational shifts in those with childhood-onset schizophrenia. These questions can only be addressed, however, with a larger sample, including younger subjects who can be scanned closer to the time of onset. It is possible that scans at the time of onset would show more striking quantitative differences.

The larger purpose of the study of childhood-onset schizophrenia is to find clues as to the very early onset of the illness. Studies of other MRI parameters, including regional myelination, temporal lobe, and cerebellar lobular measures, are in progress, and these may be found to be unusual or deviant in the population with childhood-onset schizophrenia. The present report provides the most compelling neurobiological data to date concerning the continuity between childhood-onset schizophrenia and later-onset schizophrenia.

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